

OPLS All-Atom Force Field for Carbohydrates

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ABSTRACT: The OPLS all-atom (AA) force field for organic and biomolecular systems has been expanded to include carbohydrates. Starting with reported nonbonded parameters of alcohols, ethers, and diols, torsional parameters were fit to reproduce results from *ab initio* calculations on the hexopyranoses, α,β -D-glucopyranose, α,β -D-mannopyranose, α,β -D-galactopyranose, methyl α,β -D-glucopyranoside, and methyl α,β -D-mannopyranoside. In all, geometry optimizations were carried out for 144 conformers at the restricted Hartree–Fock (RHF)/6–31G* level. For the conformers with a relative energy within 3 kcal/mol of the global minima, the effects of electron correlation and basis-set extension were considered by performing single-point calculations with density functional theory at the B3LYP/6–311 + G** level. The torsional parameters for the OPLS-AA force field were parameterized to reproduce the energies and structures of these 44 conformers. The resultant force field reproduces the *ab initio* calculated energies with an average unsigned error of 0.41 kcal/mol. The α/β ratios as well as the relative energies between the isomeric hexopyranoses are in good accord with the *ab initio* results. The predictive abilities of the force field were also tested against RHF/6–31G* results for D-allopyranose with excellent success; a surprising discovery is that the lowest energy conformer of D-allopyranose is a β anomer. © 1997 John Wiley & Sons, Inc. *J Comput Chem* 18: 1955–1970, 1997

Keywords: carbohydrates; hexopyranoses; conformational analysis; *ab initio*; force field

Introduction

In spite of the importance of carbohydrates in organic chemistry and biochemistry, they have received much less attention in the computational modeling literature than polypeptides and less functionalized organic molecules. This reflects difficulties in developing appropriate force fields owing to complexities from the size of carbohydrates, the dense array of functional groups, extreme conformational heterogeneity, and limited experimental energetic data. However, results of *ab initio* calculations for hexapyranoses have started to appear, which can provide a good basis for force field development and testing. Overall, restricted Hartree-Fock (RHF)/6-31G* calculations have been reported for 16 different conformers of D-glucopyranose by Glennon et al.,¹ Brown and Wladkoski,² and Salzner and Schleyer.³ Brown and Wladkoski also optimized three conformers of α -D-glucose at the MP2/6-31G* and BLYP/6-31G* levels and found that inclusion of the correlation effects led to variations in relative energies of less than 0.5 kcal/mol.² Barrows et al. studied two β -D-glucopyranose conformers using a very high level of theory and also noted the good accuracy of the RHF/6-31G* calculated energies.⁴

Although force field parameters have been reported for carbohydrates, much of the work has been based on *ab initio* results for component fragments with uncertain transferability to the full range of complete carbohydrate structures. Optimization of torsional parameters is the focus, while the nonbonded parameters are usually taken from the values for simple alcohols and ethers. For the AMBER all-atom (AA) force field, Merz et al.^{1,5} and Woods et al.⁶ used partial charges, which were generated for D-glucopyranose with the CHELPG procedure, and optimized torsional parameters using rotational energy profiles from RHF/6-31G* calculations on hydroxy, dihydroxy, and methoxymethyl substituted tetrahydropyrans. Similarly, Senderowitz et al. developed carbohydrate parameters for the united-atom AMBER force field and extended their parameterization to include N-acetylglucosamine.⁷ The latest parameterization of the CHARMM22 force field for carbohydrates was undertaken by Reiling et al.⁸; again, only model compounds including 1,2-ethanediol and glycerol were used to develop torsional parameters. The GROMOS force field was also ex-

tended to account for the anomeric effect in Ott and Meyer's work.⁹ New torsional parameters were introduced and optimized to reproduce *ab initio* results for dimethoxymethane and methoxymethanol. Besides these recent efforts at extending well-known force fields, there was earlier work on carbohydrate force fields in which some used^{10,11} and some did not use¹² lower level *ab initio* results to derive torsional parameters. In general, use of RHF/6-31G* or higher level *ab initio* data for the torsional parameter development is now a well-accepted procedure.^{13,14}

In this article the OPLS-AA force field is extended to treat carbohydrates.^{15,16} A requirement in OPLS-AA parameter development is accurate reproduction of the thermodynamic properties of pure organic liquids. Because many bulk properties of a liquid are mainly sensitive to the nonbonded parameters, the bonded and torsional parameters can be optimized to reproduce the molecular structures and conformational energetics from experiments and/or *ab initio* calculations. In contrast to the development of other carbohydrate force fields, the parameters presented here were obtained from fitting to *ab initio* results for complete hexopyranoses; parameters obtained from model systems like 2-hydroxytetrahydropyran were found to yield comparatively poor results. For a general force field for carbohydrates, relative energies of rotamers and isomers including anomers should be correctly reproduced. Because there is only experimental data on α/β ratios in solution and no gas-phase structural or energetic information, a data set of 144 RHF/6-31G* optimized conformers of D-glucopyranose, D-mannopyranose, D-galactopyranose, methyl D-glucopyranoside, and methyl D-mannopyranoside was created as the basis for the OPLS-AA parameter development. Barrows et al. estimated the energy of the β -D-glucopyranose in the ¹C₄ chair form to be about 6 kcal/mol higher than in the ring-flipped ⁴C₁ form with all hydroxyl groups equatorial.⁴ Due to this large energy difference, only the ⁴C₁ forms of the hexopyranoses were considered here.

As demonstrated, for example, with Monte Carlo simulations of complexes between a cyclophane host and substituted benzenes, relative free energies of binding can be calculated with the OPLS force fields in good agreement with experimental values.¹⁷ The OPLS force field was also found to reproduce *ab initio* calculated interaction energies between 1,2-ethanediol and an acetate ion.¹⁸ Such complexes reflect common motifs for

the interactions of carbohydrates with the side chains of glutamate and aspartate residues in proteins. Carbohydrate–protein binding plays a central role in intercellular recognition, and it is a target for further study with the OPLS-AA force field.^{19,20}

Computational Methods

AB INITIO AND DENSITY FUNCTIONAL THEORY (DFT) CALCULATIONS

Full geometry optimizations were carried out for the hexopyranoses using the GAUSSIAN/94 program²¹ with RHF theory and the 6–31G* basis set. The performance of this method for calculating relative energies of conformers and torsional profiles is analyzed below and in refs. 22 and 23. Single-point calculations on the RHF/6–31G* geometries and full geometry optimizations were also carried out at the B3LYP/6–311 + G** level.²⁴ Such hybrid *ab initio* and DFT methods using nonlocal exchange correlation functionals are known to give results similar to very high level *ab initio* calculations.^{25,26} In particular, it was found that B3LYP/6–311G** calculations give conformer energies for 1,2-ethanediol that are in good agreement with results obtained at the CCSD(T)/cc-pVDZ//MP2/cc-pVDZ level.^{25,27} RHF/6–31G* results for 1,2-ethanediol also compare well with those from the higher level *ab initio* calculations.²⁸

FORCE FIELD CALCULATIONS

Molecular mechanics calculations for the hexopyranoses were performed with the BOSS program and the OPLS-AA force field.^{16,29} The force field consists of harmonic terms for bond stretching and angle bending, a Fourier series for each dihedral angle, and Coulomb and Lennard–Jones interactions between atoms separated by three or more bonds as shown in eqs. (1)–(4). The intramolecular nonbonded interactions between atoms separated by three bonds (1,4 interactions) are reduced by a factor of 2. Furthermore, standard combining rules are used such that $A_{ij} = (A_{ii}A_{jj})^{1/2}$ and $C_{ij} = (C_{ii}C_{jj})^{1/2}$. The A and C parameters may be expressed in terms of Lennard–Jones σ s and ϵ s as $A_{ii} = 4\epsilon_i\sigma_i^{12}$ and $C_{ii} = 4\epsilon_i\sigma_i^6$. For geometry optimizations in BOSS, the

Fletcher–Powell algorithm was used with a convergence criterion of 1×10^{-5} kcal/mol.

$$E_{\text{bond}} = \sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2, \quad (1)$$

$$E_{\text{angle}} = \sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2, \quad (2)$$

$$V(\phi) = \frac{V_1}{2}[1 + \cos(\phi + f_1)] + \frac{V_2}{2}[1 - \cos(2\phi + f_2)] + \frac{V_3}{2}[1 + \cos(3\phi + f_3)], \quad (3)$$

$$E_{\text{nb}} = \sum_{i < j} (q_i q_j e^2 / r_{ij} + A_{ij} / r_{ij}^{12} - C_{ij} / r_{ij}^6). \quad (4)$$

TORSIONAL PARAMETER OPTIMIZATION

The torsional parameters (V_1 , V_2 , V_3) were optimized using Fitpar.³⁰ By varying all the torsional parameters using simplex and Fletcher–Powell algorithms, this program minimizes the difference between the *ab initio* and force field calculated energies obtained for sets of structures [eq. (5)].

$$\sum_{\text{compounds}} \sum_{\text{conformers}} |E_{\text{ab initio}} - E_{\text{force field}}| \quad (5)$$

In this optimization procedure, all V s of different parameter types (e.g., C—C—O—H and O—C—C—O) are optimized together, although individual V s can also be fixed to a value, usually zero. This results in a better overall fit than from individual optimization of the torsional parameters. The fitting of the torsional parameters is an iterative procedure. The first set of parameters is obtained using the *ab initio* optimized structures. With this set of torsional parameters, the geometries are then optimized with the force field. The next set of torsional parameters is obtained using these force field calculated geometries. The structures are computed again and the torsional parameters are reoptimized until the values of the torsional parameters converge.

Results and Discussion

AB INITIO CONFORMATIONAL ANALYSIS

Geometry optimizations were carried out at the RHF/6–31G* level for 144 conformers of D-glucopyranose **1**, D-galactopyranose **2**, D-mannopyranose **3**, methyl D-glucopyranoside **4**, and

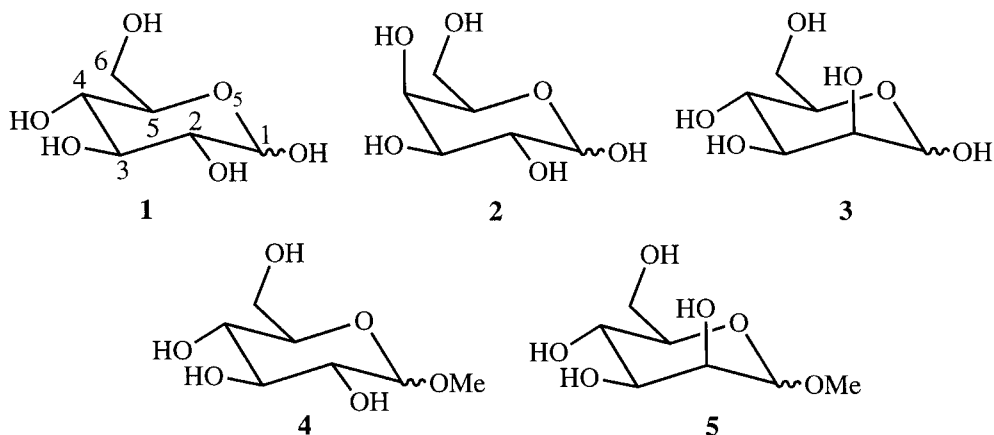


FIGURE 1. Structures of hexopyranoses.

methyl D-mannopyranoside 5 (Fig. 1). The conformations considered differences in the configuration at the anomeric carbon (α or β), the direction of the hydrogen-bond network (clockwise or counterclockwise as viewed from the β face), the O—C—O—H or O—C—O—C exoanomeric angle, and the O—C5—C6—OH and C5—C6—O—H dihedral angles, which define the orientation of the hydroxymethylene group. In Table I the energies and values of these geometrical variables are given for those 44 conformers with a relative energy within 3 kcal/mol of the global minimum for pyranoses 1–3 and pyranosides 4 and 5. These 44 RHF/6–31G* relative energies and structures were used to determine the torsional parameters for the force field, as discussed below. The resultant energies are listed relative to the lowest energy conformation for the two series, 2a and 4b.

In Figure 2 the lowest energy conformers of 1–5 are illustrated as “ball and stick” models. In all of these cases the lowest energy conformer is an α anomer. The structures show the different hydrogen-bond patterns. A hydrogen-bond network oriented clockwise is preferred for galactopyranose 2, mannopyranose 3, and mannopyranoside 5; whereas the counterclockwise arrangement is preferred for the glucoses 1 and 4. These gas-phase preferences are largely dictated by maximization of the number of intramolecular hydrogen bonds and the favoring of α anomers by the anomeric effect. The hydrogen-bonding patterns may not be dominant in crystal structures and in aqueous solution, where intermolecular hydrogen bonds must also be accommodated.³¹

The energy differences between the hexopyranoses caused by differences in orientation of the hydroxymethylene group were investigated with

the clockwise and counterclockwise hydrogen-bond networks for C1–C4. Examples of the different orientations of the hydroxymethylene group are shown for α -D-glucopyranose with a counterclockwise hydrogen-bond network and for α -D-galactopyranose with a clockwise network in Figure 3. These are the preferred hydrogen-bond patterns of 1 and 2. The corresponding conformers of 1 with a clockwise and of 2 with a counterclockwise oriented hydrogen-bond network are at least 0.9 kcal/mol higher in energy (Table I). For gauche[−] (1a, 2a), gauche (1b, 2i), and trans (1c, 2j) orientations of the O—C5—C6—O dihedral angle, the C5—C6—O—H angle is positioned to obtain additional hydrogen bonds. For 1 the three conformers are essentially isoenergetic because the C6OH unit engages in one hydrogen bond in each case. However, for 2 the C6OH unit forms hydrogen bonds with both the ether oxygen and the C4OH group in 2a, while it only forms one hydrogen bond in 2i and 2j. The extra hydrogen bond not only makes 2a significantly more favorable than the other conformers of 2, but also the lowest energy structure for 1–3. Optimizations were also performed for the corresponding conformations of methyl D-glucopyranoside 4. Similar relative energies were obtained for 4a–c and 1a–c (Table I). The same conformational analysis was performed for the β anomers of 1–4. The relative energies of the three different O—C5—C6—O orientations are found to be similar as for the α anomers (e.g., 1a–c and 1h–j). Therefore, whether a hexose is a hemiacetal or acetal does not influence the energetics of these different orientations of the hydroxymethylene group.

In all hexopyranoses with an equatorial hydroxy group at C4 (1, 3–5), the three different

TABLE I.
Calculated Relative Energies of Hexopyranoses 1–5 at Various Levels.

	B3LYP ^a	HF ^b	FF ^c	O—C—O—X (°) ^d	O—C—C—O (°)	C—C—O—H (°)	Anomer / H-Bond Network ^e	Opt. B3LYP ^f
1a	0.57	0.86	1.13	63.3	−57.6	58.2	α / cc	
1b	0.58	0.94	0.94	61.7	59.2	−59.1	α / cc	
1c	0.57	0.74	0.84	62.1	166.4	53.3	α / cc	0.65
1d	1.48	1.66	1.28	−164.9	−63.1	61.0	α / cl	
1e	1.71	1.67	1.93	−164.7	−176.5	−178.2	α / cl	
1f	2.18	2.08	2.10	178.9 ^g	−176.6	−178.5	α / cl	
1g	1.81	1.94	2.45	−152.2 ^h	−176.5	−178.3	α / cl	
1h	1.31	1.86	2.43	−61.6	−57.5	57.0	β / cc	
1i	1.20	2.06	1.82	−62.9	59.3	−58.1	β / cc	1.51
1j	1.42	1.91	2.09	−58.5	166.7	53.5	β / cc	
1k	2.34	2.99	2.64	38.7	166.7	53.3	β / cc	
2a	0.00 ⁱ	0.00 ^j	0.00	−165.5	−58.8	61.3	α / cl	0.00 ^k
2b	1.56	1.89	2.97	63.6	−55.1	−47.1	α / cc	
2c	0.77	0.94	0.65	62.1	61.1	−62.5	α / cc	
2d	1.55	0.97	0.94	62.7	−171.7	79.9	α / cc	
2e	2.53	2.36	2.35	62.1	172.3	159.6	α / cc	
2f	2.10	2.29	6.14	69.1	−59.0	59.2	α / cl	
2g	2.07	2.55	3.16	−61.1	61.4	−61.8	β / cc	2.21
2h	2.77	2.42	3.37	−53.0	−170.9	80.7	β / cc	
3a	1.35	0.99	1.18	58.5	−64.7	56.4	α / cl	1.43
3b	2.94	2.93	2.94	57.2	58.4	−56.8	α / cl	
3c	1.96	1.44	1.32	58.1	−178.1	179.3	α / cl	
3d	2.95	2.96	2.99	53.3	166.7	52.7	α / cc	
3e	3.18	2.61	2.70	30.0 ^l	−178.4	179.3	α / cl	
3f	1.95	1.45	1.46	60.0 ^l	−178.0	179.3	α / cl	
3g	2.70	2.69	1.50	90.0 ^l	−177.6	179.6	α / cl	
3h	2.03	2.22	2.28	−48.7	−58.5	54.7	β / cc	
3i	1.81	2.32	0.93	−49.2	59.7	−58.9	β / cc	
3j	1.72	1.86	1.21	−45.0	166.8	53.8	β / cc	
3k	1.49	1.61	1.81	74.4	−64.5	58.8	β / cl	1.64
3l	1.92	1.82	1.49	72.2	−177.2	−179.4	β / cl	
3m	2.36	2.12	1.70	60.0 ^l	−177.1	−179.4	β / cl	
3n	2.29	2.49	2.51	90.0 ^l	−177.2	−179.3	β / cl	
4a	0.22	0.11	0.32	67.7	−57.4	57.7	α / cc	
4b	0.00 ^m	0.00 ⁿ	0.00	64.9	58.8	−59.9	α / cc	0.00 ^o
4c	0.16	0.00	0.06	67.0	166.5	53.3	α / cc	
4d	3.05	2.90	2.95	72.1	−62.7	58.9	α / cl	
4e	3.33	2.94	3.44	71.8	−177.6	179.6	α / cl	
4f	1.11	1.23	2.04	−68.4	−57.3	56.5	β / cc	1.16
4g	1.21	1.46	1.52	−68.8	59.5	−57.8	β / cc	
4h	1.04	1.29	1.88	−66.7	166.9	53.3	β / cc	
5a	1.97	0.99	0.58	66.3	−177.9	179.3	α / cl	1.80
5b	2.81	2.49	2.04	63.6	166.8	52.6	α / cc	
5c	1.93	1.62	1.66	−62.4	166.9	53.7	β / cc	1.85

^a Relative energies obtained at B3LYP / 6–311 + G** // RHF / 6–31G* in kcal / mol.^b Relative energies obtained at RHF / 6–31G* // RHF / 6–31G* in kcal / mol.^c Relative energies obtained with the OPLS-AA force field in kcal / mol.^d For **1–3** X = H and for **4** and **5** X = CH₃.^e cc stands for a counterclockwise and cl for a clockwise hydrogen-bond network.^f Relative energies obtained at B3LYP / 6–311 + G** // B3LYP / 6–311 + G** in kcal / mol.^g C2—C1—O—H angle fixed at 300°.^h C2—C1—O—H angle fixed at 330°.ⁱ Energy = −687.4010763 au.^j Energy = −683.3352339 au.^k Energy = −687.405803135 au.^l Fixed dihedral angle.^m Energy = −726.7106723 au.ⁿ Energy = −622.3613721 au.^o Energy = −626.715476 au.

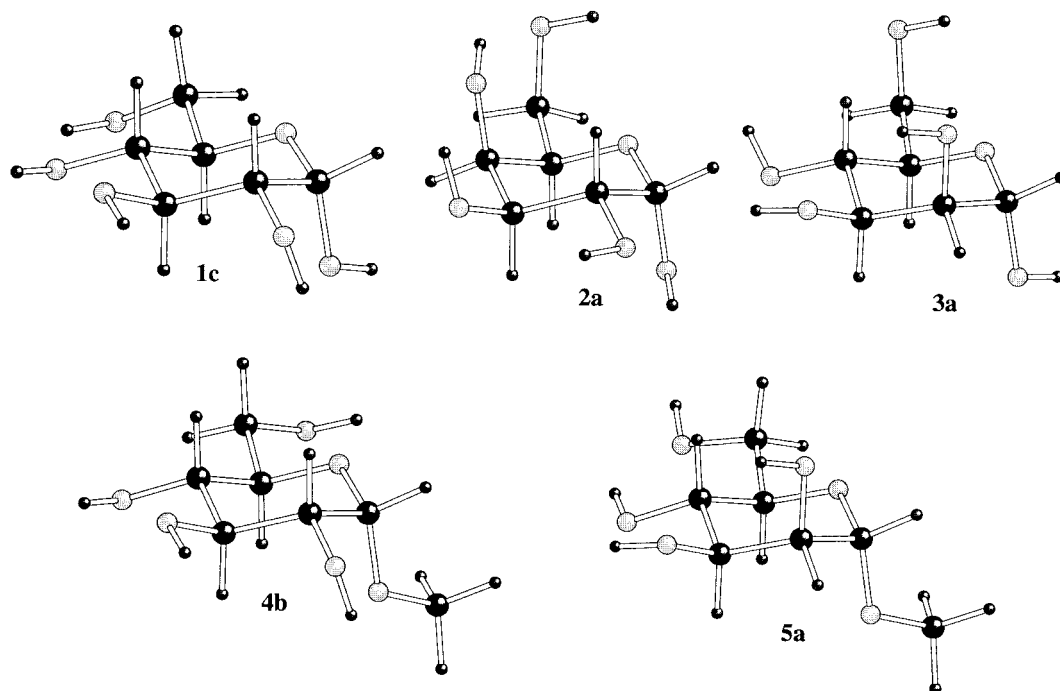


FIGURE 2. Hexopyranose conformations lowest in energy from the *ab initio* calculations.

orientations of the hydroxymethylene group have about the same energy in a counterclockwise hydrogen-bond network; in a clockwise network the gauche orientation for O—C5—C6—O is 1.5–2 kcal/mol higher in energy than for gauche[−] and trans (e.g., 3a–c). Because D-mannopyranose 3 has relative energies similar to D-glucopyranose 1 and 1 has relative energies similar to methyl D-glucopyranoside 4 for conformers, which differ in their orientation of the hydroxymethylene group, it is expected that the relative energies for the three orientations of the hydroxymethylene group are also the same in methyl D-mannopyranose 5. Therefore, only structures with the conformation anticipated to be preferred for the hydroxymethylene group were investigated in 5. By considering the three different orientations of the hydroxymethylene group for 1–4 in the two different orientations of the hydrogen-bonding network and the two different anomers, 48 conformers were obtained. An additional 12 structures were optimized for 5.

The effects of changes in conformation at C1 were extensively investigated for D-glucopyranose 1 and D-mannopyranose 3. Structures were optimized for alternative orientations of the 1-hydroxy group for the α and β anomers with clockwise and counterclockwise hydrogen-bond networks and with the hydroxymethylene group oriented to hydrogen bond with the C4OH. Examples of

gauche (1c, 1k, 3l), bans (1e), and gauche[−] (1j, 3j) orientations of the O—C—O—H dihedral angle are shown in Figure 4. For α anomers, gauche and gauche[−] are favored by the exoanomeric effect; however, gauche[−] structures, which have the hydroxyl hydrogen pointing inside the pyranose ring, are not competitive. For β anomers, gauche and gauche[−] are again favored, but now gauche is typically higher in energy by about 1 kcal/mol (e.g., 1k vs. 1j). Basically, from Table I it is apparent that among the low energy structures, the O—C—O—H dihedral angle is predominantly gauche for α structures and gauche[−] for β structures. However, hydrogen bonding can override these preferences as in the striking case of 2a, the most stable of all for 1–3, which has a trans O—C—O—H angle.

For the clockwise network, energy profiles for the rotation of the 1-OH group were calculated in 30° increments for α and β anomers of both D-glucopyranose and D-mannopyranose. The lack of a hydrogen bond between the hydroxyl groups at C1 and C2 in many of the structures caused only five α conformers (1f, 1g, 3e, 3f, 3g) and two β conformers (3m, 3n) to be low enough in energy to be included in the optimization of the torsional parameters. The calculation of the four rotational profiles provided 48 rotamers. Other geometry variations, where one hydroxy group was rotated to eliminate a hydrogen bond or where other ori-

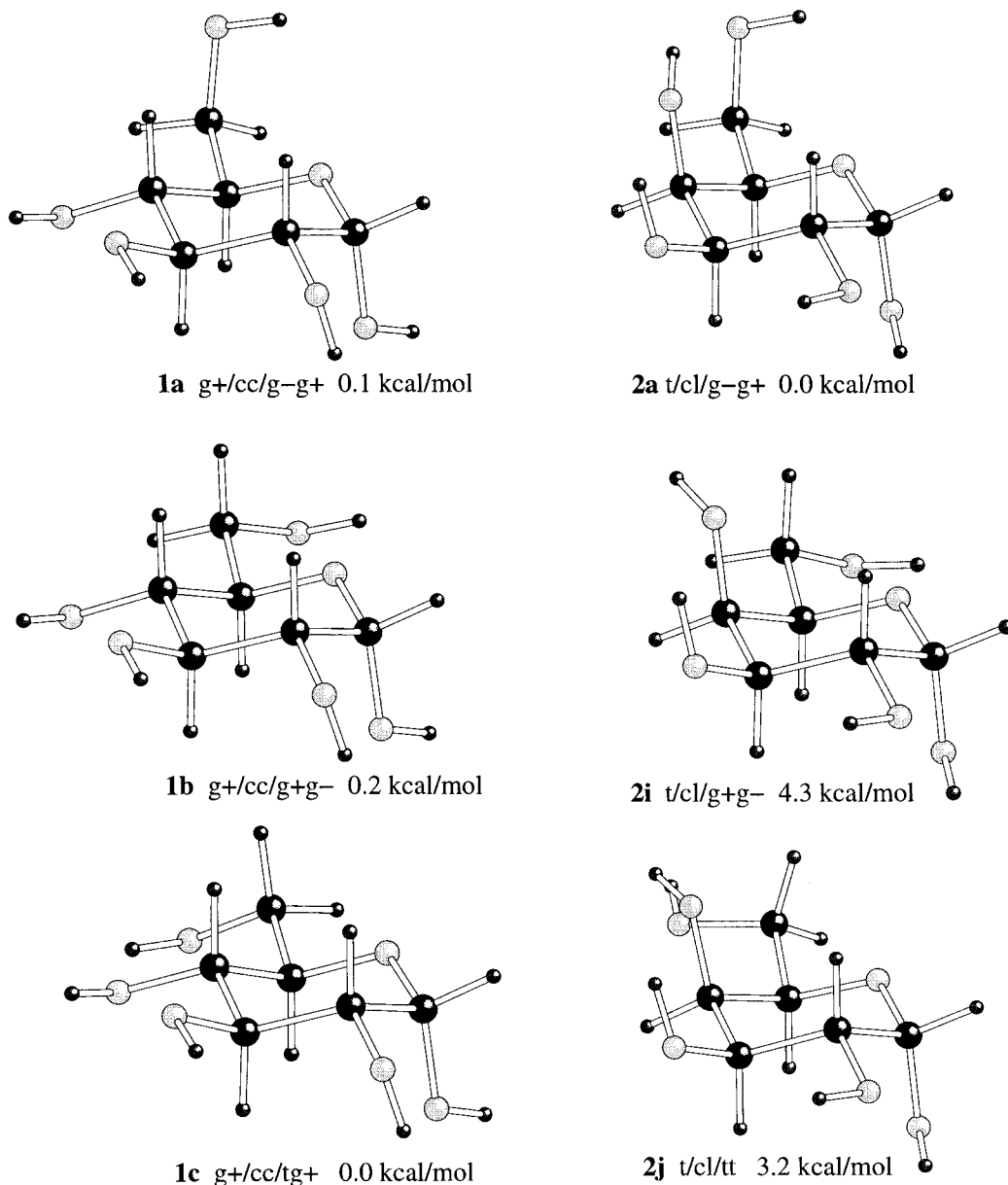


FIGURE 3. Different orientations of the hydroxymethylene group in α -D-glucopyranose **1** and α -D-galactopyranose **2**. The label for each conformation indicates the O—C—O—H dihedral angle, the orientation of the hydrogen-bond network, the O—C5—C6—O and the C5—C6—O—H dihedral angles. t means trans, g + means gauche⁺, and g – means a gauche[–] conformation.

entations of the methoxy group in **4** and **5** were investigated, led to the remaining structures. These structures were all high in energy, but brought the total number of optimized structures to 144: 52 for **1**, 15 for **2**, 46 for **3**, 19 for **4**, and 12 for **5**.

To evaluate the accuracy of the RHF/6-31G* relative energies, B3LYP/6-311 + G** single-point calculations were first performed on the RHF/6-31G* optimized structures. The relative

energies obtained at the two levels are compared in Table I. The average unsigned error between the higher level single-point and the RHF/6-31G* energies is 0.30 kcal/mol. Furthermore, the α and β anomers lowest in energy from the single-point calculations for hexopyranoses **1–5** were optimized fully at the B3LYP/6-311 + G** level. The average unsigned errors in comparing these results to the single-point and RHF/6-31G* results are

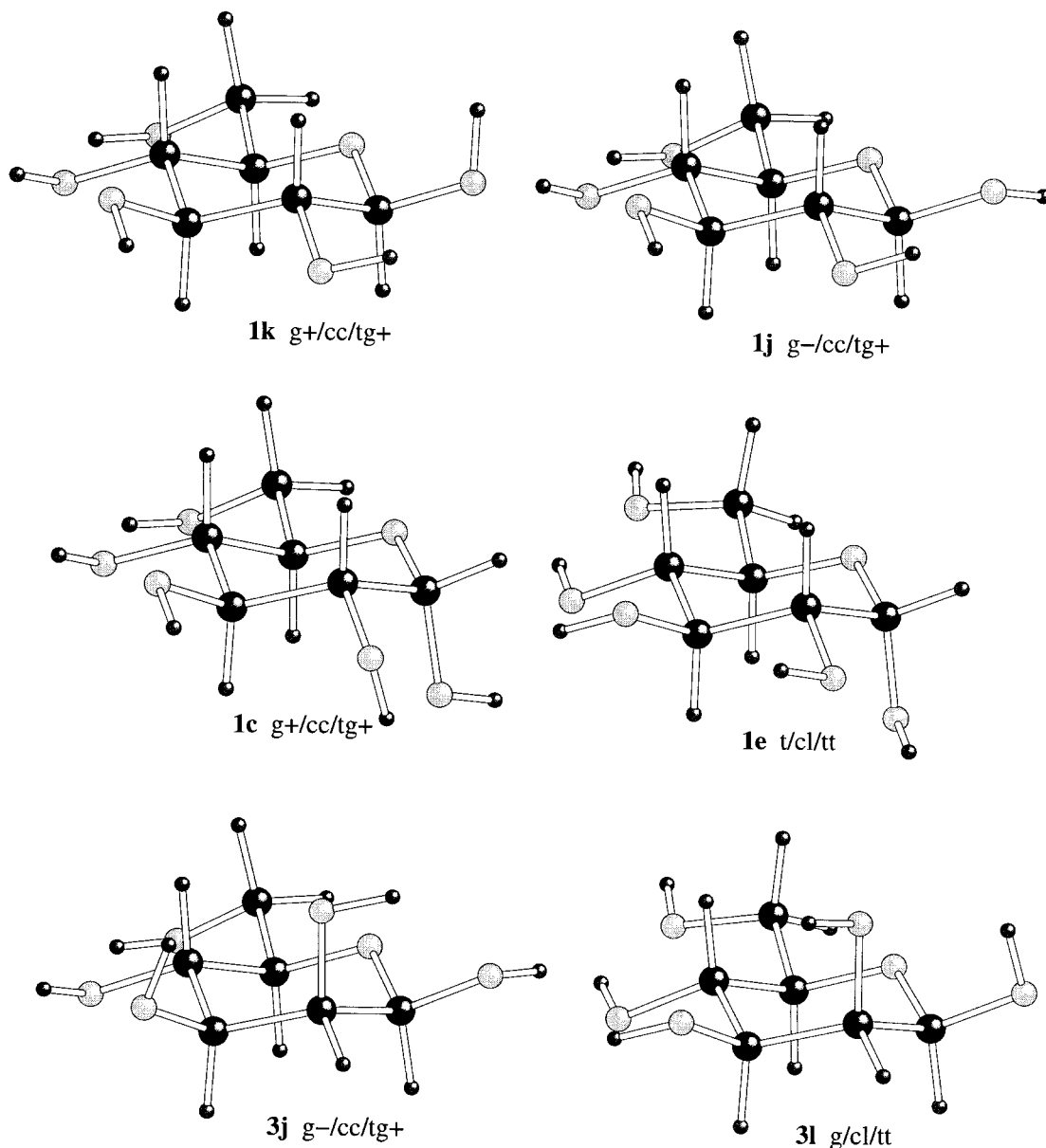


FIGURE 4. Different orientations of the 1-OH group in D-glucopyranose **1** and D-mannopyranose **3**. The conformational labels are described in the caption of Figure 3.

0.13 and 0.32 kcal/mol (Table I). The largest discrepancy by far between the B3LYP/6-311 + G** and the RHF/6-31G* calculated structures is 0.86 kcal/mol for methyl D-mannopyranoside **5a** versus **4b** (see Fig. 2). In view of the wide range of hydrogen-bonding patterns, the level of accord is remarkable. This reconfirms the quality of the RHF/6-31G* results and also shows that improvement is difficult without an inordinate expenditure of computer time, as noted by Barrows et al.⁴

NONBONDED PARAMETERS

For the purposes of assigning nonbonded parameters, the hexopyranose structures were divided into three parts. Consistent with the usual approach in the OPLS force fields to facilitate construction of larger molecules, each fragment is required to be charge neutral. The hydroxymethylene group of a hexopyranose represents the alcohol part. The partial charges (Fig. 5) and the Lennard-Jones parameters (Table II) optimized for

TABLE II.
OPLS-AA Lennard-Jones Parameters
for Carbohydrates.

Atom	σ (Å)	ε (kcal / mol)	Obtained from
H on C	2.50	0.030	Alkanes
C	3.50	0.066	Alcohols
O in CH ₂ OH	3.12	0.170	Alcohols
O in CHOH	3.07	0.170	Diols
H in OH	0.00	0.000	Alcohols
O in C—O—C	2.90	0.140	Ethers

standard alcohols are used in this case.¹⁶ The second part contains the C2–C4 polyol fragment. The nonbonded parameters used here were adopted from those optimized to reproduce the properties of liquid 1,2-ethanediol.¹⁸ These parameters are slightly different than the simple alcohol parameters; the σ of the oxygen atom is smaller and the magnitudes of the charges on the oxygen and hydrogen atoms are larger than for simple alcohols (Table II, Fig. 5). The last part is the acetal (R = Me) or a hemiacetal (R = H) fragment. The partial charges and the Lennard-Jones parameters used for the oxygen atom in the ring and for the anomeric oxygen atom of pyranosides (R = Me) are the same as for ethers.¹⁶ The partial charge on the carbon atom of the anomeric center is assigned to obtain a neutral molecule, where the charge of the attached hydrogen atom is 0.1 e for both R = H

and R = Me. The acetal parameters were shown in Monte Carlo simulations to reproduce the thermodynamic properties of liquid dimethoxymethane and 1,3-dioxolane well.¹⁶

The present charge model for hexopyranoses can be compared to CHELPG derived charges,³² which were obtained from the RHF/6–31G* calculations for 1–5. As noted above, such charges have been used in earlier force fields.^{1, 5, 6} Because CHELPG charges depend on the investigated conformation, it was also interesting to check the range of the CHELPG charges for the hexopyranoses. Comparison of the OPLS-AA charges in Figure 5 and the ranges covered by the CHELPG charges in Figure 6 shows that the magnitudes of the OPLS-AA charges are generally on the low end of the range. Although there are obvious limitations with fixed charge models, it is not clear that the ranges of charges suggested by the CHELPG calculations are accurate.³³ The OPLS-AA charges reflect less polarization than the average 6–31G* CHELPG charges. In other work, OPLS-AA charges have been optimized to reproduce the thermodynamic properties of liquid glycerol and do show a somewhat larger charge on the oxygen (–0.73) and the hydrogen (+0.465) atom. However, significantly poorer fits were obtained for the conformational energetics of the hexopyranoses with the charges from glycerol than with the diol based charges.

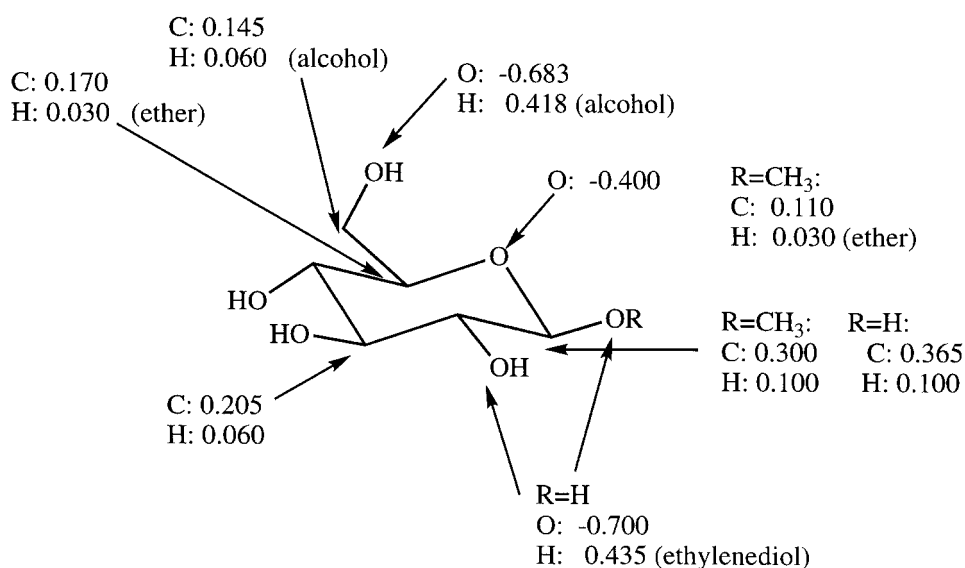


FIGURE 5. OPLS-AA partial charges in electrons for carbohydrates.

BOND STRETCHING AND ANGLE BENDING PARAMETERS

The OPLS-AA parameters for bond stretching and angle bending have largely been taken from the AMBER AA force field¹⁴ with some modifications.¹⁶ For acetals we defined an additional atom type, CO, for an anomeric carbon. A shorter r_{eq} is used for bonds to CO than to ether carbon owing to the anomeric effect.³⁴ Otherwise, standard AMBER atom types are used: CT for saturated carbon, OS and OH for ether and hydroxyl oxygens, and HC and HO for hydrogens on carbon and oxygen. Although all of the parameters have been reported elsewhere,^{12, 14, 16, 18, 34} they are collected in Tables III and IV for clarity.

TORSIONAL PARAMETER OPTIMIZATION

Of the 144 conformers optimized at the RHF/6-31G* level, the 44 lowest energy structures in Table I were used to fit the torsional

TABLE III.
OPLS-AA Bond Stretching Parameters
for Carbohydrates.

AMBER Types	r_{eq} (Å)	K_r (kcal / mol Å ²)
CT-OS	1.410	320.0
CT-OH	1.410	320.0
CO-OS	1.380	320.0
CO-OH	1.380	320.0
CT-CT	1.529	268.0
CT-CO	1.529	268.0
CT-HC	1.090	340.0
CO-HC	1.090	340.0
OH-HO	0.945	553.0

TABLE IV.
OPLS-AA Angle Bending Parameters
for Carbohydrates.

AMBER Types	θ_{eq} (°)	K_θ (kcal / mol rad ²)
CT-CT-CT	112.70	58.35
CT-CT-CO	112.70	58.35
CT-CT-HC	110.70	37.50
CO-CT-HC	110.70	37.50
CT-CO-HC	110.70	37.50
CT-CT-OH	109.50	50.00
CO-CT-OH	109.50	50.00
CT-CT-OS	109.50	50.00
CT-CO-OS	109.50	50.00
CT-CO-OH	109.50	50.00
CT-OS-CO	109.50	60.00
CT-OS-CT	109.50	60.00
CT-OH-HO	108.50	55.00
CO-OH-HO	108.50	55.00
HC-CT-HC	107.80	33.00
HC-CT-OS	109.50	35.00
HC-CT-OH	109.50	35.00
HC-CO-OS	109.50	35.00
HC-CO-OH	109.50	35.00
OS-CO-OS	111.55	92.60
OS-CO-OH	111.55	92.60

parameters. Inclusion of all 144 structures causes unacceptable degradation of the fit for the low energy structures to accommodate the high energy ones. The first seven sets of Fourier coefficients in Table V were taken from the OPLS-AA values for alkanes, alcohols, and ethers.¹⁶ The final six sets of Fourier coefficients in Table V are the new ones, which were optimized for carbohydrates. There are two O—C—C—O parameter sets: OH—C—C—OS for dihedral angles to the ring oxygen atom

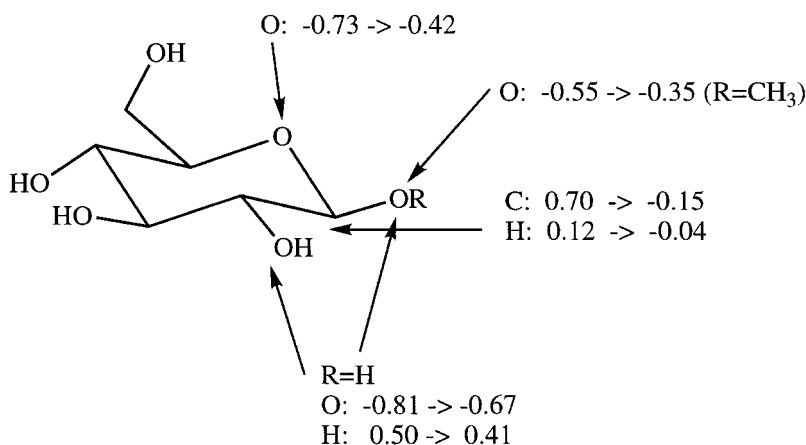


FIGURE 6. Ranges of RHF / 6-31G* CHELPG charges in electrons for hexopyranoses 1-5.

TABLE V.
OPLS-AA Torsional Parameters (kcal/mol)
for Carbohydrates.

Type	V_1	V_2	V_3
H-C-C-H	0.0	0.0	0.318
H-C-C-C	0.0	0.0	0.366
C-C-C-C	1.74	-0.157	0.279
H-C-C-O	0.0	0.0	0.468
H-C-O-H	0.0	0.0	0.450
H-C-O-C	0.0	0.0	0.760
C-O-C-C	0.650	-0.250	0.670
C-O-C-O	-0.375	-1.358	0.004
O-C-O-H	-1.257	-1.806	0.003
C-C-C-O	-1.336	0.0	0.0
C-C-O-H	2.674	-2.883	1.026
OH-C-C-OS	4.319	0.0	0.0
OH-C-C-OH	9.066	0.0	0.0

and OH—C—C—OH for all dihedral angles between oxygen atoms of the hydroxyl groups. As found during the torsional parameterizations for glycerol and 1,2-ethanediol, a single V_1 term is sufficient in these cases. It was also found that the torsional parameters describing the C—C—O—H torsion of simple alcohols do not optimally describe the energetics of carbohydrates, so a new set of Fourier coefficients was determined. Similarly, the C—C—C—O parameters for straight chain alcohols were found to be inappropriate in the highly functionalized context of the pyranoses and required reparameterization. Finally, the O—C—O—H and O—C—O—C parameters are critical in establishing the α/β ratio and were optimized.

COMPARISON OF FORCE FIELD AND *AB INITIO* RELATIVE ENERGIES

In the following, the energetic results from the *ab initio* and force field calculations are compared and any important structural differences are also noted. The relative energies for the hexopyranoses are given in Table I. The average unsigned error and the root mean square (RMS) deviation between the RHF/6-31G* and the force field calculated energies for all 44 conformers are 0.41 and 0.75 kcal/mol. In view of the structural complexities of the hexopyranoses and the simplicity of the force field, the quality of the fit is gratifying. The predictive abilities of the force field are considered below for allopyranoses. As with the *ab initio* and the DFT methods, the force field finds the hexopyranose conformations **2a** and **4b** to be lowest in

energy (Fig. 2). The relative energies from the force field and from the RHF/6-31G* calculations for the lowest energy conformers of **1**, **3**, and **5** (**1c**, **3a**, and **5a**) are also within 0.5 kcal/mol.

The three low energy conformers of α -D-glucopyranose, **1a–c**, differ in the orientation of the hydroxymethylene group. The force field correctly reproduces the fact that their relative energies fall within a narrow range, ca. 0.2 kcal/mol, in spite of the differences in hydrogen bonding (see Fig. 3). Conformers **1d** and **1e** have the hydrogen-bond network oriented in the opposite, clockwise direction and are also correctly computed to be only a little higher in energy. The β anomers **1h–j** differ in their orientation of the hydroxymethylene group as for the α anomers **1a–c**. The largest deviation of the force field calculated energies from the RHF/6-31G* ones for **1h–j** is 0.57 kcal/mol.

The effects of the epimerization at C4 for D-galactopyranose on the energetics of the different orientations of the adjacent hydroxymethylene group are important to consider. Structures **2b–d** show the same conformation for the hydroxymethylene group as the D-glucopyranose conformations **1a–c**. The relative energies of **2c** and **2d** from the force field compare well to the RHF/6-31G* ones, while conformation **2b** is too high in energy by 1 kcal/mol. In comparison to **2d**, which has a gauche C5—C6—O—H dihedral angle, **2e** has a trans C5—C6—O—H angle, which breaks the hydrogen bond with the C4 hydroxyl group. The force field closely reproduces the RHF/6-31G* energies for these two structures and their difference of 1.4 kcal/mol. With the trans arrangement, the hexopyranose could donate a hydrogen bond in solution to a water molecule. The balance between intra- and intermolecular hydrogen bonding is, consequently, sensitive to such differences. The largest deviation between the force field and the RHF/6-31G* energies is found for **2f**; **2f** is obtained from **2a** by changing the orientation of the trans O—C—O—H angle to gauche, which restores the exoanomeric preference but destroys the C1OH—C2OH hydrogen bond. With RHF/6-31G* the difference in energy is 2.3 kcal/mol, while the force field yields a difference of 6.1 kcal/mol. All hexopyranose conformers that lack a hydrogen bond between the hydroxyl groups at C1 and C2 are relatively high in energy, although it is still desirable to obtain the correct energetics in view of the expected potential of hydration to preferentially stabilize the conformers with fewer internal hydrogen bonds. The problem with the energetics for the rotation of the O—C—O—H

angle is caused by the scaling of the 1,4 electrostatic interactions. The 1,4 interaction between the hydroxyl hydrogen at C1 and the ether oxygen in the ring is scaled, while its interaction with the oxygen atom of the hydroxyl group at C2 is not scaled (Fig. 7). This imbalance of the electrostatic interactions cannot be fully compensated by the O—C—O—H torsional parameters. If a gauche O—C—O—H orientation is made more favorable, the α -D-galactopyranose conformers **2b–d** become lower in energy than **2a**, the lowest energy conformer from the *ab initio* calculations. Therefore, all the force fields widely used for protein modeling and adjusted to handle carbohydrates, which use such a scale factor, are going to have similar problems. The scaling is done to allow the use of the same nonbonded parameters for intra- and intermolecular interactions.¹⁶ This simplifying choice probably needs to be abandoned in future efforts.

The lowest energy conformer of D-mannopyranose, **3a**, is 0.99 and 0.25 kcal/mol higher in energy than the lowest energy conformers of **2** (**2a**) and **1** (**1c**) from the RHF/6–31G* calculations; these results compare well to the values of 1.18 and 0.34 from the force field. Conformations **3a–c** show again the different orientations of the hydroxymethylene group. With a clockwise hydrogen-bonding network, these conformations are not equal in energy as for **1a–c**, which have a counterclockwise network. The ca. 2 kcal/mol higher energy for **3b** than **3a** and **3c** is well represented by the force field. The relative energies from the force field for the β anomers **3h–n** are also mostly reasonable. However, **3i**, which is similar to **3j** in Figure 4 except the hydroxymethylene group is rotated to hydrogen bond with the ring ether oxygen, is too low in energy by 1.39 or 0.88 kcal/mol in comparison to the RHF/6–31G* or B3LYP results. The repulsive orientation between the C1 and C6 hydroxyl groups in **3i** is uncommon and may be underestimated by the force field. In this way, with the force field **3i** ends up 0.25 kcal/mol lower in energy than **3a**, which should be the

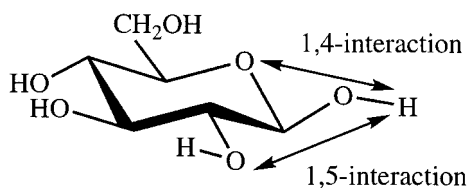


FIGURE 7. Illustration of 1,4 and 1,5 interactions between the C1 hydroxyl hydrogen and oxygen atoms.

lowest energy conformer for **3**. The difference between the lowest energy α and β anomers, **3a** and **3k**, at the RHF/6–31G* level is, however, correctly obtained.

The RHF/6–31G* relative energies of the hexopyranosides **4** and **5** are very well reproduced by the force field. The largest discrepancy is 0.81 kcal/mol for **4f**. The conformations lowest in energy are **4a–c**. These have the same orientations of the hydroxymethylene group as in **1a–c** for which the force field also performs well. **4d** and **4e** have the opposite, clockwise hydrogen-bond network and are ca. 3 kcal/mol higher in energy from all calculations. The β conformers **4f–h** are also found to be 1–2 kcal/mol higher in energy than their α analogs, **4a–c**. Furthermore, all methods find the lowest energy conformer for the mannopyranoside **5** to be higher in energy than for the lowest energy conformer of the glucopyranoside **4**, although the difference varies from 0.58 kcal/mol from the force field to 0.99 and 1.80 kcal/mol from the RHF/6–31G* and B3LYP optimized calculations. Conformation **5a** has a clockwise hydrogen-bond network, whereas conformation **5b** has a counterclockwise one. The difference in energy between these two conformers is 1.5 kcal/mol from both the force field and RHF/6–31G* calculations. Although only gauche orientations of the O—C—O—Me angle were included for the parameter optimization, the ones with a trans orientation, which are at least 4 kcal/mol higher in energy, are also accurately reproduced by the force field. This is important for the treatment of the different orientations between the individual monosaccharide units in polysaccharides.

In Table VI computed relative energies from the OPLS-AA, AMBER, and CHARMM force fields are compared for six α - and six β -D-glucopyranose conformations. Four of the structures were over the 3 kcal/mol limit from **2a** and were not included in Table I. For both the α and β anomer, these structures cover the three orientations of the hydroxymethylene group with the clockwise and counterclockwise hydrogen-bond networks. The AMBER¹ and CHARMM¹² force fields give RMS deviations of 2.82 and 1.54 kcal/mol to the RHF/6–31G* results, respectively. The RMS error for the OPLS force field is 0.81 kcal/mol, which shows important and expected improvement. The largest individual errors are 8.2, 4.1, and 1.7 kcal/mol from the AMBER, CHARMM, and OPLS-AA force fields, respectively.

The hexopyranoses studied here differ only in the configuration of the stereocenters at C1, C2,

TABLE VI.
Relative Energies for D-Glucopyranose Obtained with Different Force Fields.

	HF ^a	OPLS ^b	AMBER ^c	CHARMM ^d	O—C—O—H (°)	O—C—C—O (°)	C—C—O—H (°)	Anomer / H-Bond Network ^e
1a	0.12	0.29	0.4	0.8	63.3	−57.6	58.2	α / cc
1b	0.20	0.10	1.0	0.5	61.7	59.2	−59.1	α / cc
1c	0.00	0.00	0.0	0.0	62.1	166.4	53.3	α / cc
1d	0.92	0.44	0.5	0.5	−164.9	−63.1	61.0	α / cl
1l	2.77	3.97	1.2	1.6	−165.6	61.0	−50.7	α / cl
1m	0.85 ^f	0.07	1.8	0.1	−165.2	−178.8	−77.7	α / cl
1h	1.12	1.59	9.3	0.7	−61.6	−57.5	57.0	β / cc
1i	1.32	0.98	3.4	3.2	−62.9	59.3	−58.1	β / cc
1j	1.17	1.25	1.1	5.3	−58.5	166.7	53.5	β / cc
1n	3.84	2.54	5.3	3.8	167.8	−62.8	60.5	β / cl
1o	5.38	4.60	4.8	4.8	167.6	59.5	−54.2	β / cl
1p	4.20	2.48	7.1	2.5	165.8	−178.4	−79.8	β / cl

^a RHF/6-31G* // RHF/6-31G* relative energies in kcal/mol.^b Relative energies from the OPLS-AA force field in kcal/mol.^c Relative energies from the AMBER force field (ref. 1).^d Relative energies from the CHARMM force field (ref. 12, data from ref. 1).^e cc stands for a counterclockwise and cl for a clockwise hydrogen-bond network.^f Although this conformer is within 3 kcal/mol of **2a**, it was not in the set used for the parameter optimization.

and C4. D-Allopyranose **6**, which differs from D-glucopyranose by epimerization at C3, was also investigated with RHF/6-31G* calculations in order to test the force field's predictions on structures that were not used in the parametrization. In Figure 8 six α and six β anomers of D-allopyranose **6** are shown with clockwise and counterclockwise hydrogen-bond networks, where the O—C5—C6—O dihedral angle is oriented trans, gauche, and gauche[−]. The RHF/6-31G* energies still relative to structure **2a** are given with the OPLS-AA values in parentheses. The force field and RHF/6-31G* calculations both find structures **6g**, **6h**, and **6i** to be the lowest in energy and in a narrow range. The *ab initio* results have **6i** as the lowest and 0.68 kcal/mol above D-galactopyranose conformer **2a**, while the force field prefers **6h** over **6i** by 0.43 kcal/mol. These results are striking because **6g**, **6h**, and **6i** are all β anomers. The geometries of the individual hydrogen bonds appear particularly good in these structures. As found in D-glucopyranose, the relative energies for the different orientations of the hydroxymethylene group are well reproduced when the hydrogen-bond network is counterclockwise (**6a–c** and **6g–i**). The energies of the corresponding conformations with a clockwise network, which are higher in energy, compare less well to the *ab initio* relative energies with deviations in the 1–2 kcal/mol range. The average unsigned error for the force field

predictions on all 12 conformers is 0.83 kcal/mol, and it is only 0.39 kcal/mol for the four conformers with relative energies below 3 kcal/mol. Thus, the investigation of D-allopyranose demonstrates that the OPLS-AA force field shows good predictive ability for conformers of a hexopyranose that was not in the original data set and that even has unusual low energy structures.³⁵

After completion of this work, Csonka et al. reported *ab initio* results for 14 conformers of α-L-fucose (α-L-6-deoxygalactopyranose).³⁶ In comparison to RHF/6-31G* // RHF/6-31G* results, optimizations with the OPLS-AA force field correctly identify the three lowest energy conformers; they have relative energies of 0.0, 1.92, and 2.71 kcal/mol from the *ab initio* calculations; the OPLS-AA results are 0.0, 1.69, and 0.83 kcal/mol.

Conclusion

The conformational analysis of hexopyranoses with *ab initio* calculations showed that similar relative energies are obtained at the RHF/6-31G and B3LYP/6-311 + G** levels and provided a data base for optimization of torsional parameters for the OPLS-AA force field. With the addition of a minimal set of torsional parameters, it was possible to extend the force field to provide a good representation of the conformational energetics of

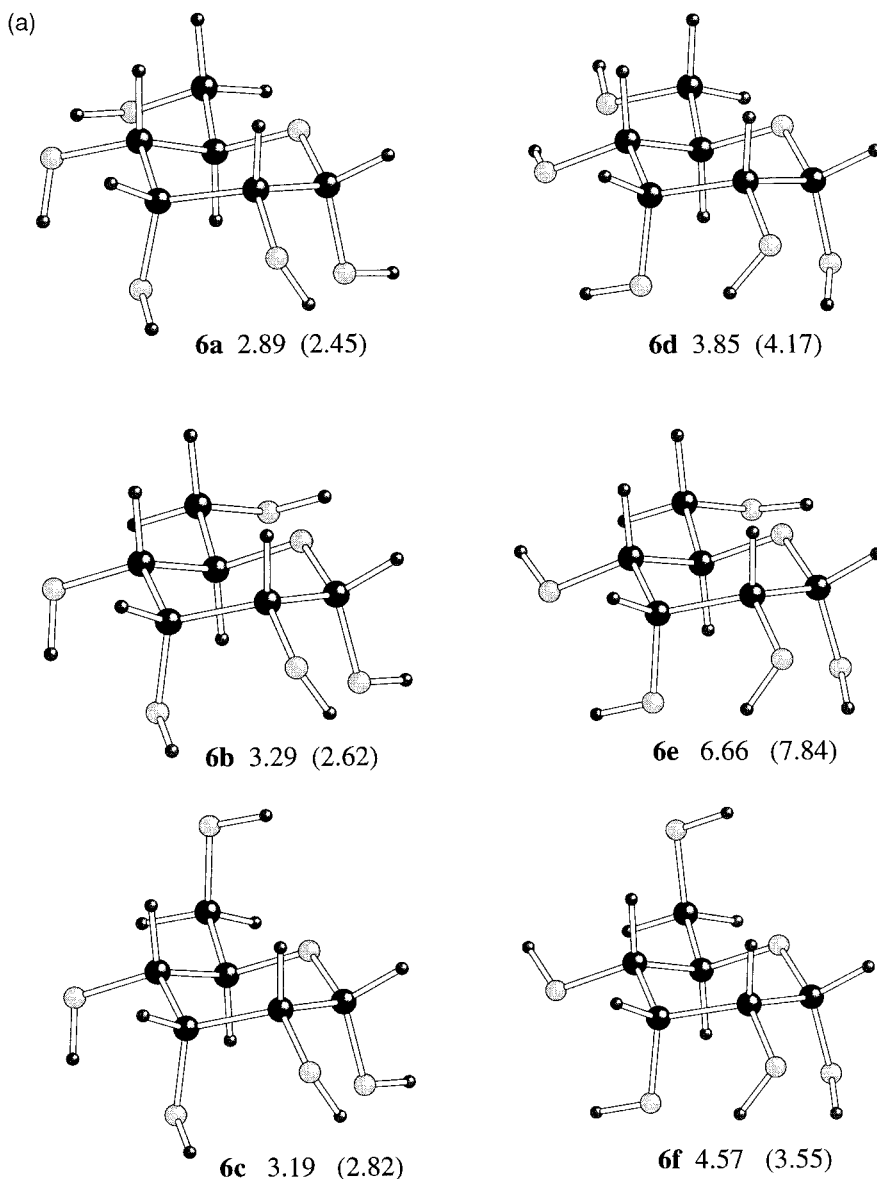


FIGURE 8. Energies of (a) α and (b) β D-allopyranose conformations obtained from RHF/6-31G* calculations and from the OPLS-AA force field (in parentheses). All energies are in kilocalories/mole relative to the energies of α -D-galactopyranose conformer 2a.

the monosaccharides. The OPLS-AA force field was shown to perform significantly better than available alternatives for D-glucopyranose. The force field is able to reproduce well the relative energies of different hexopyranoses, the α/β ratios, and hydrogen-bonding variations determined at the RHF/6-31G* level. The parameters were also found to correctly predict the relative energies for the unusual low energy conformations of D-allopyranose. Further testing of the potential functions is underway. However, the present results indicate that it is now possible to perform well-

founded calculations on many interesting problems such as solvent effects on the conformational equilibria of carbohydrates and the binding of carbohydrates by hosts including proteins.

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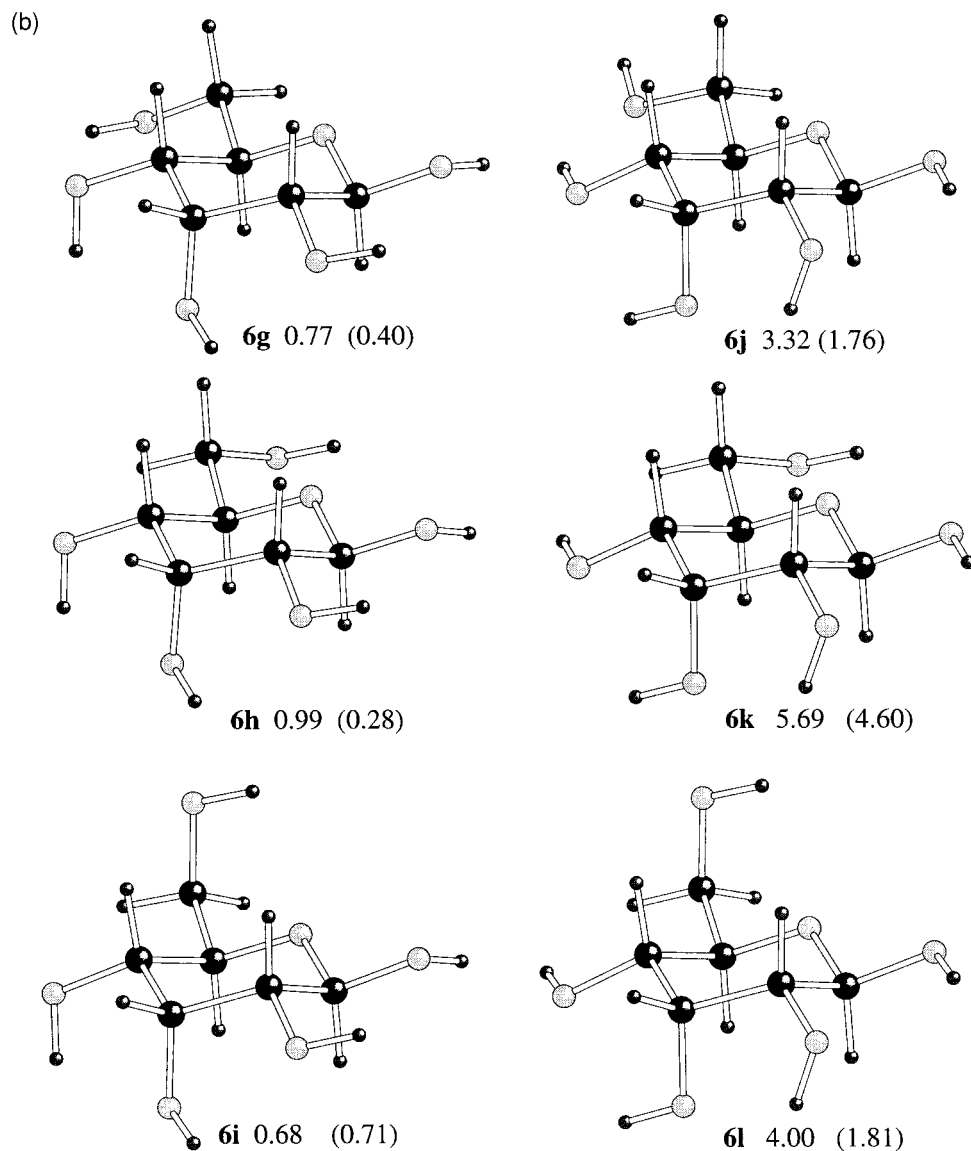


FIGURE 8. (Continued)

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